REMARKS

Reconsideration of this patent application is respectfully requested in view of the foregoing Amendments, and the following remarks.

The Amendments to this patent application are as follows.

The Specification on page 1 was amended to include a "Cross-Reference to Related Applications," which includes the appropriate application numbers and filing dates for the PCT international patent application, and for the German priority patent applications.

The claims were amended by cancelling claims 4, 7 and 8 without prejudice, and by amending claims 1, 5, 12, 13, 14 and 15. The dependency of claim 5 has been corrected.

Regarding claim 11, Claim 11 refers to a generically engineered organism. As the animal of claim 1 could be genetically engineered, claim 11 is consistent with the organism of claim 1.

Claim 12 has been made consistent with claim 1, by Amendment.

Concerning claim 13, claim 13 now has an antecedent basis, because it has been amended to be dependent from claim 11.

Concerning claim 14, a further step has been added which is directed to the removal of high molecular weight peptides, as disclosed on page 3, paragraph 4 of the present Specification. This further step has been inserted before the step of "directly detecting..."

It is important to note that according to the present invention, not only are some peptides being measured, but all peptides are measured which can be detected. Therefore, an Amendment was made to further restrict claim 5. The wording added is set forth on page 2 in the middle of the last paragraph, of the present Specification, as follows:

> "It is possible to detect single peptides directly by a measuring technique or to detect several peptides by a measuring technique or even all the low molecular weight peptides present in the sample which can be detected by a measuring technique."

The measuring technique is MALDI mass spectrometry in claim 1, is chromatography in claim 14, and is mass spectrometry in

claim 15. The added language is that "all low molecular weight peptides present in the sample which can be detected by MALDI mass spectrometry are detected" in claim 1.

Similar language was added for claims 14 and 15.

For all of the above reasons, it is firmly believed that the Specification, and all of the claims are now in complete compliance with the requirements of 35 U.S.C. 112. Withdrawal of this ground of rejection is respectfully requested.

The Applicants comment upon the prior art rejections of the claims as follows.

Tellerova detected only peptides with a molecular weight higher than 4,000 Da, whereas the present invention detects peptides having a molecular weight of up to 30,000 Da, that is from about 50 to 30,000 Da. *Tellerova* detects peptides from 4,000 to about 1 million Da or more.

Tellerova does not measure all peptides present in the sample but instead only tests for peptides with a molecular weight above 4,000 Da.

As explained by *Tellerova* on page 201, first line, no individual peptides are measured. The peaks 0 to 5 represent categories of peptides. Therefore, no single peptides are measured.

Shibata does not disclose that all peptides are analyzed but instead only discloses glucose-containing glycopeptides or glycoproteins. There is no limitation on the molecular weight of the analyzed peptides. There is no statement of an analysis of the obtained data or relation to a control. Therefore, no differential peptide display is obtained by *Shibata*.

Mabuchi differs from the claimed invention in that peptides are not measured directly but only after derivatisation with fluorescamine; see page 294, first paragraph.

The focus of the analysis in *Mabuchi* are peptides with molecular weights below 1,000 Da, whereas the present invention covers all peptides up to 30,000 Dalton.

The peptides are not directly analyzed by *Leber*. There is an "elution peak..." which has been further analyzed by thin layer chromatography. This resolves 5 peptides which have to be detected by application of ninhydrin; see page 1077, last line.

Therefore, no peptides are detected by chromatography.

Only one peak has been further analyzed by thin layer chromatography. Therefore, not all "peptides" are analyzed.

Klosse discloses that peptides are not measured directly but only after derivatisation with ninhydrin or folin-lowry reagent.

No peptides above 15,000 Da are included in the analysis.

Nagase discloses that only two compounds are analyzed: The aminoacid hydroxyproline (hyp) and a single peptide prolyl hydroxyprolin. Therefore, no low molecular weight peptides up to 30,000 Da are measured and not all peptides of the sample are detected.

Kodama discloses that only very special compounds are analyzed (imino dipeptides). The molecular weights are below 300, therefore, no peptides between the molecular weight of 300 to 30,000 are measured.

Not all peptides of the sample are detected. There is no relation of the analysis to a reference, so no differential peptide display is obtained.

Charpentier discloses that only dipeptides are analyzed, that is peptides with a molecular weight up to 399 (see table 1 on page 306). No peptides with a molecular weight up to 30,000 Dalton are measured.

The data of the analysis are not related to a reference and no differential peptide pattern is obtained. Not all peptides of the sample are detected.

According to the Examiner, the claims 1, 4 to 9 and 11 to 13 are unpatentable over any of the above-mentioned documents in view of *Jiminez* or *Wang*.

Wang was published in the *Journal of Biological Chemistry on December 30, 1996,* i.e. after the priority date of August 13, 1996, of the present patent application. Because the priority claim is valid, *Wang* is not prior art against this application.

Jiminez, Journal of Neurochemistry, 1994, 404 to *407* discloses the use of MALDI mass spectrometry. The Examiner relies on *Jiminez* to show that MALDI MS is a sensitive measurement technique but it does not cure the deficiency of the primary references. None of them discloses the claimed method of the present invention wherein:

(a) all detectable peptides from a sample are measured;

(b) the measurement comprises the low molecular weight peptides up to 30,000 Da;

(c) the peptides are directly detected, and

(d) related to a reference.

Therefore, the combination of the primary references with *Jiminez*, would not produce the method of the present invention.

For all these reasons, none of the prior art references provide an identical disclosure of the claimed invention. Hence the present invention is not anticipated under 35 U.S.C. 102. Withdrawal of this ground of rejection is respectfully requested.

In summary, the above amendments to the claims distinguish the claims over the combined teachings of all the prior art references under 35 U.S.C. 103.

Withdrawal of this ground of rejection is respectfully requested.

A prompt notification of allowance is respectfully requested.

Respectfully submitted,

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Enclosure: 1) Copy of Petition Three Month Extension of Time

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on June 18, 2003..

Maria Guastella

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